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10/009,151	04/16/2002	Takashi Shigematsu	13723-002001	8643

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EXAMINER	
LUM, LEON YUN BON	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 02/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,151	SHIGEMATSU ET AL.	
	Examiner	Art Unit	
	Leon Y. Lum	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *November 3, 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-64* is/are pending in the application.

4a) Of the above claim(s) *22-26 and 30-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-29 and 58-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendments filed November 6, 2005 and November 11, 2005 are acknowledged and have been entered.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 61 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claim has been newly added to provide the limitation wherein "the melted solution of denatured and stabilized lipoprotein does not form flocculation." However, this limitation is not present in the specification and one of ordinary skill in the art, having read the specification, would not recognize that melted solution of denatured and stabilized lipoprotein would necessarily exclude any flocculation.

Flocculation is well known to one of ordinary skill in the art as an aggregate or accumulation of material. While Applicants have disclosed that anti-coagulants have

been added to serum samples (see page 13, lines 12-20) that my presumably prevent any aggregation, Applicants have not provided sufficient evidence that supports their claim of a lack of flocculation. The data presented in the Figures and described in the disclosure provide absorbance readings between samples. However, the absorbance readings could include systemic clumping of biomolecules that would constitute flocculation. It is known from the prior art that aggregation of biomolecules can cause turbidity, which reduces the optical clarity through a sample. See Magneson et al (US 5,547,873), column 1, lines 23-28. Optical density is the ratio of the intensities of emitted and transmitted light, and can determine the presence or absence of flocculation. See Magneson et al, column 4, lines 5-10. However, the specification and drawings in the instant application do not provide any such data or equivalent that would clearly indicate a lack of flocculation in the claimed samples. One of ordinary skill in the art at the time of the invention would therefore not be able to ascertain whether the samples are free of flocculation.

Due to the lack of convincing evidence and support for newly added claim 61, the instant claim is rejected as introducing new matter.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 27-29, 58-59, 61, and 63-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The instant claim recites three steps in succession starting with the phrase "freezing a solution containing lipoprotein to produce a frozen solution of lipoprotein" (see line 3), followed by the phrase "melting the frozen solution to produce a melted solution of denatured and ***stabilized lipoprotein***" (see lines 4-5), and finally followed by the phrase "freeze-drying the melted solution to produce the denatured and stabilized lipoprotein in powder form (see lines 6-7). The claim appears to indicate the act of freezing and melting a solution containing lipoprotein provides the claimed "stabilized lipoprotein", but the specification does not support this process. It is clear from the disclosure that the step of "freeze-drying the melted solution" provides the stabilizing mechanism. See page 5, line 28 to page 6, line 12, which states that "***by freeze-drying*** such artificially denatured lipoproteins...it is made possible to improve conspicuously such denatured lipoproteins in ***stability of prolonged preservation*** and consequently accomplish the objection of the present invention." In addition, see page 7, lines 14-19, which states "To be specific, the object mentioned above is accomplished by a method for producing stabilized denatured lipoprotein by artificially denaturing lipoprotein, thereby obtaining denatured lipoprotein and ***freeze-drying the denatured lipoprotein, thereby stabilizing the denatured lipoprotein***."

However, the specification does mention that a stabilizer can be added prior to the freezing step, which would therefore provide a denatured ***and*** stabilized lipoprotein

solution after the freezing and melting steps. See page 24, lines 13-23. The specification therefore does provide support for a "denatured and stabilized lipoprotein" prior to the freeze-drying step, but it is not apparent from the current claim language that a stabilizer is added prior to the first freezing step. Since the addition of a stabilizer is a crucial step in providing for the claimed "denatured and stabilized lipoprotein" in the second step, the claim is required to include a step of adding the stabilizer. The lack of this step therefore presents an omission of essential subject matter and the instant claim is rejected as being vague and indefinite.

7. In claim 28, it is unclear whether the instant claim is intended to (1) introduce a method step requiring the application of a DLH3 antibody or the FOH1a/DLH3 hybridoma, or (2) recite an inherent characteristic of the denatured lipoprotein. If situation (2) is intended, the claim is improper for failing to further limit the parent claim (claim 27) since an actual method step has not been claimed. For the purposes of prosecution, the Examiner interprets the instant claim as claiming situation (2) since there is no indication, either in the claims or in the specification, as to how the DLH3 antibody or the FOH1a/DLH3 hybridoma would be applied in a method step. Since situation (2) is interpreted for the instant claim, an anticipation of the denatured lipoprotein in parent claim 27 would necessarily anticipate the instant claim since the claim language only suggests that the denatured lipoprotein would inherently possess the stated characteristics.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 27-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Kamarei (US 4,749,522).

Kamarei reference teaches that prior to an extraction process isolating biomolecules from tissue, various methods in combination can be performed to the tissue, wherein two such methods in combination can be freeze-thaw treatment and freeze-drying. See column 8, lines 39-43 and 51-52. In addition, Kamarei teaches that the tissue can be blood plasma (i.e. solution containing lipoprotein) and the biomolecule is lipoprotein. See column 6, line 32 and column 7, line 64. While the reference itself is directed towards a supercritical fluid extraction process, the reference sufficiently discloses teaching of steps that anticipate the instant claims. For example, the combination of the freeze-thaw and freeze-drying processes would necessarily have to be performed in the order of (1) freeze-thaw and then (2) freeze-drying (i.e. freezing and melting a solution containing lipoprotein; freeze-drying the melted solution), since the opposite order produces dried material that lacks water in order to perform the thawing process. Furthermore, although Kamarei teaches numerous biomolecules that can individually be isolated from numerous tissue types, the disclosure of many

embodiments does not necessarily render the reference as incapable of performing the claimed limitation. In fact, the courts have stated that, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

In the instant reference, the step of applying biological tissue samples to either freeze-thawing or freeze-drying are well known to one of ordinary skill in the art. Since blood plasma is one type of tissue that can be frozen, one of ordinary skill in the art would recognize that blood plasma could be chosen as a tissue to perform the necessarily sequential steps of freeze-thawing and freeze-drying. The instant claim is therefore anticipated.

With respect to claim 28, see the explanation for the 112, 2nd paragraph rejection supra on the instant claim.

10. Claims 27-29, 59-60, and 62-64 are rejected under 35 U.S.C. 102(b) as being anticipated by Magneson et al (US 5,547,873).

Magneson et al reference teaches the method of preparing stabilizing proteins for long term dry storage, by teaching the sequential steps of adding anti-coagulant solution to a sample of blood plasma (i.e. adding an anti-coagulating agent preceding the freezing step), subjecting the blood plasma to several freeze/thaw processes (i.e. freezing and melting a solution containing lipoprotein), and then lyophilizing the blood

plasma after the last thawing step (i.e. freeze-drying the melted solution of lipoprotein), wherein the lyophilized product contains LDL. See column 2, lines 39-44; column 4, line 30 to column 5, line 18; and Table 1.

With respect to claim 28, see the explanation for the 112, 2nd paragraph rejection supra on the instant claim.

With respect to claim 63, Magneson et al teach the blood plasma includes serum. See column 2, lines 34-38.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 58 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Magneson et al (US 5,547,873) in view of Proksch et al (US 4,216,117).

Magneson et al reference has been disclosed above and additionally teaches that trehalose or sucrose sugar (i.e. stabilizing agent) is added to thawed blood plasma solution prior to lyophilization, wherein the resulting reconstituted lipoprotein solutions have improved optical clarity over control solutions without the sugars. See column 5, lines 3-7 and Table 1. However, Magneson et al fail to teach that the stabilizing agent is added prior to the freezing step.

Proksch et al reference teaches the step of adding polyhydroxy cryoprotective agents such as lactose and sucrose to lipoprotein diluent prior to freezing, in order to ensure the stability and integrity of the lipoprotein solution and to also prevent turbidity from occurring after thawing. See column 4, lines 48-68.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Magneson et al with the step of adding polyhydroxy cryoprotective agents such as lactose and sucrose to lipoprotein diluent prior to freezing, as taught by Proksch et al, in order to ensure the stability and integrity of the lipoprotein solution and to also prevent turbidity from occurring after thawing. Both Magneson et al and Proksch et al references teach the addition of sugars (i.e. trehalose, sucrose of Magneson et al and lactose, sucrose of Proksch et al) to reduce turbidity in lipoprotein solutions. Since the references teach in combination that optical clarity is achieved regardless of the order in which the sugars are added and the lipoprotein solutions are frozen, it would have been obvious to one of ordinary skill in the art to recognize that Proksch et al provides an obvious equivalence to the method of Magneson et al with respect to the order to adding sugar to a solution of lipoprotein. In addition, since Proksch et al teaches an additional benefit of stabilizing the lipoprotein solution by including sugars, there is sufficient motivation to combine the teachings of Proksch et al with the method of Magneson et al.

Response to Arguments

15. Applicant's arguments, see page 8 of the response, filed November 3, 2006, with respect to the enablement rejection of claim 28 have been fully considered and are persuasive. The rejection under 112, 1st paragraph of claim 28 has therefore been withdrawn.

16. Applicant's arguments with respect to claims 27-29 and 58-64 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leon Y. Lum whose telephone number is (571) 272-2878. The examiner can normally be reached on weekdays from 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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